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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/884,873 06/30/97 COOK

P ISIS-2202

HM22/1204

EXAMINER

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ART UNIT	PAPER NUMBER
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1627

18

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks**BEST AVAILABLE COPY**

Office Action Summary

Application No. 08/884,873	Applicant(s) Cook
Examiner Maurie E. Garcia, Ph. D.	Group Art Unit 1627

Responsive to communication(s) filed on Aug 17, 2000

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle* 1035 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

Claim(s) 2-13, 24-30, and 33-36 is/are pending in the application

Of the above, claim(s) 6, 13, 27-30, and 33-36 is/are withdrawn from consideration

Claim(s) _____ is/are allowed.

Claim(s) 2-5, 7-12, and 24-26 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Response filed August 17, 2000 (Paper No. 17) is acknowledged. Claims 32 and 14-19 were cancelled, claims 2-13 and 24-26 were amended and claims 33-36 were added. Therefore, claims 2-13, 24-30 and 33-36 are pending. Further consideration has necessitated new rejections. Since the new rejections were not brought about by the amendment to the claims, the case is maintained in non-final status. Also, please note the change in examiner.

Election/Restriction

2. Applicant's election of species in the paper filed February 7, 2000 (Paper No. 15) is also acknowledged. The present examiner would like to address some issues on the record concerning this election.

3. First, because applicant did not distinctly and specifically point out any supposed errors in the election of species, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claims 6 and 13 (which were pending at the time of the species election) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species. Election was made **without** traverse in Paper No. 15. Please note

that claim 6 is being withdrawn because applicant's elected species are compounds that have *different* tether moieties and claim 13 is being withdrawn because applicant's elected species are compounds that *do not* have at least one functionalizable atom of the scaffold that is chemically blocked.

5. Newly submitted claims 34-36 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: applicant's elected species are compounds that have an *unsaturated* core structure (pyrimidine) and *do not* have chemical substituents that are further modified. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 34-36 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

6. Claims 27-30 were previously withdrawn from consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention (see Response filed November 2, 1998 (Paper No. 7), page 7). The examiner notes that although applicant mentions that claims 27-30 have been cancelled, it does not appear that there were directions to do so in the Response and as such, these claims remain pending in the instant case. Correction is requested.

7. Therefore, claims 2-5, 7-12, 24-26 and 33 are examined on the merits.

8. The examiner would like to point out that a search of applicants *specific* elected species did not result in identification of any prior art. Thus, the search was extended as per MPEP § 803.02 “should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species”. The examiner has extended the search to include all compounds containing the pyrimidine scaffold structure as set forth in claim 33 (compound I).

Withdrawn Rejections

9. All rejections previously of record are withdrawn.

New Rejections
Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 2-5, 7-12, 24-26 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Applicant's claims are directed to a mixture of chemical compounds that have a chemical substituent (L) attached thereto. The claims use both specific and generic terminology to define these L groups. The claims lack written description in regards to the generic terminology used, specifically the following terms: (1) Metal coordination group; (2) Conjugate group; (3) Drug; (4) Group capable of hydrogen bonding. These terms are very broad and lack adequate written description in the instant specification.

There are a virtually infinite number of compounds that would fall within the claimed definition of L being a (1) Metal coordination group; (2) Conjugate group; (3) Drug; (4) Group capable of hydrogen bonding. These chemical substituents (L) could encompass such very different moieties such as peptides, oligonucleotides and organic and inorganic molecules. However, the instant specification discloses the preparation of compounds containing only a very limited number of such chemical substituents (L). The instant description also discloses only a few examples of how such chemical substituents (L) can be linked to the scaffold molecule.

The disclosure is neither representative of the claimed genus, nor does it represent a substantial portion of the claimed genus. Moreover, the claimed genus encompasses members which are yet to be prepared or envisioned. This further evidences that instant disclosure does not constitute support for the claimed genus or a substantial portion thereof.

12. Claims 2-5, 7-12, 24-26 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specifically defined chemical substituents (L), does not reasonably provide enablement for any chemical substituent (L) that is a (1) Metal coordination group; (2) Conjugate group; (3) Drug; (4) Group capable of hydrogen bonding. Additionally, the specification is not enabled for any mixture having antibacterial effect and/or having various activities (claims 24-26). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is clear from applicant's specification how one might practice this invention with specific mixtures of compounds either taught in the specification or known in the art; however, there is insufficient guidance as to how to make/use any mixture. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the level of one of ordinary skill;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

For the sake of clarity, the two issues defined above are treated separately with regards to the Wands Factors.

Issue 1: The specification, while being enabling for specifically defined chemical substituents (L), does not reasonably provide enablement for any chemical substituent (L) that is a (1) Metal coordination group; (2) Conjugate group; (3) Drug; (4) Group capable of hydrogen bonding.

The breadth of the claims and the nature of the invention: The claims recite (in part) that the chemical substituents (L) are a (1) Metal coordination group; (2) Conjugate group; (3) Drug; (4) Group capable of hydrogen bonding. No other limitations on these groups are given and, as such, this could read on a wide variety of structures. Such represents very broad scope. **The state of the prior art and the level of predictability in the art:** Compounds that are (1) Metal coordination groups; (2) Conjugate groups; (3) Drugs; (4) Groups capable of hydrogen bonding were known at the time of filing; however, only certain of these compounds were known (i.e. those of specific structure). The instant specification gives no guidance to permit one of skill in the art to devise strategies

for attachment of *any* of these groups to a compound having the recited heterocyclic scaffold and also how to use such compounds (and mixtures thereof). The structures of possible variants are sufficiently diverse and one of ordinary skill would not be able to predict their structures. The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. The existence of working examples and the quantity of experimentation needed to make or use the invention based on the content of the disclosure: Applicants have only provided examples of chemical substituents that are small organic molecules (having defined structures); therefore further research would be necessary to make or use the invention for *any* type of (1) Metal coordination groups; (2) Conjugate groups; (3) Drugs; (4) Groups capable of hydrogen bonding. The instant specification gives one skilled in the art no indication that one could use *any* such chemical substituent and have a reasonable expectation of success. Therefore, the practice of the full scope of the invention would require undue experimentation.

Issue 2: The specification is not enabled for any mixture having antibacterial effect and/or having various activities (claims 24-26).

The breadth of the claims and the nature of the invention: Claims 24-26 state that the claimed mixtures "exhibit sensible antibacterial effect" or have a certain activity. No limitations on the specific chemical substituents used in the compound mixture is given. The state of the prior art and the level of predictability in the art: Compounds that exhibit antibacterial effects or the claimed activity that have a pyrimidine core were known at the time of filing;

however, only limited numbers of such compounds were known. The instant specification gives no guidance to permit one of skill in the art to devise strategies for synthesis of *any* mixture of compounds that might function in such a fashion. The structures of possible variants are sufficiently diverse and one of ordinary skill would not be able to predict which structures would have the desired activity.

The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. The existence of working examples and the quantity of experimentation needed to make or use the invention based on the content of the disclosure: In claims 24-26 the functional limitations set forth in the claims are simply not supported by the instant disclosure. The disclosure does not teach how to make/use such mixtures. No testing of the libraries using the pyrimidine scaffold was performed and the libraries made do not resemble any known pyrimidine compounds that are antibacterials (see, for example, WO 96/16046 for representative examples of such compounds). Thus the instant specification gives one skilled in the art no indication that one could use *any* mixture of such compounds and have a reasonable expectation of success. Therefore, the practice of the full scope of the invention would require undue experimentation.

New Rejections
Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 5 and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- A. Claim 5 depends from claim 33, which recites "a common heterocyclic scaffold bearing functionalizable atoms". However, claims 5 recites "said heterocyclic scaffold has at least three functionalizable atoms" which is deemed to be indefinite. The language in claim 5 that states that the scaffold **has** at least three functionalizable atoms is confusing and the language "said heterocyclic scaffold bears at least three functionalizable atoms" is suggested.
- B. The term "sensible" in claim 24 is a relative term which renders the claim indefinite. The term "sensible" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.
- C. The term "forms a library having activity" in claims 25 and 26 renders the claim indefinite. It is completely unclear how the mixture "forms a library" and how the "library" has activity. Is the "library" (ie mixture) to have the activity as a whole, or simply one member thereof? Clarification is requested.

New Rejections
Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 2-5, 7-12 and 33 are rejected under 35 U.S.C. 102(a) as being anticipated by Gordeev et al (WO 96/33972).

Gordeev et al disclose methods for synthesizing libraries of pyrimidine compounds (see Abstract). The library compounds of Gordeev et al have the claimed heterocyclic scaffold and substitution pattern (see page 34-35 and more specifically page 81) and are substantially homogeneous (page 35, bottom). The library compounds are made in a pooled format (see page 84, lines 18-28), for example, a pool of 21 pyrimidines is made and tested. This reads directly on the limitation of a mixture of at least 6 compounds and the further limitations of claims 2 and 3. All compounds are present in at least some of the pools and the compounds are synthesized at a purity (see page 81) where the mixture would be close to equimolarity. The pyrimidine compounds of Gordeev et al have at least three functionalizable atoms, at least one of which is nitrogen (see pages 81-85). In the compounds of Gordeev et al the tethers can be considered to be bonds for two of the side groups and the amine moiety could be considered a tether moiety (NHR¹). This meets the limitations of claims 5 and 7-10. The building blocks of

the library comprise various leaving groups (see page 83), reading on the limitations of claims 11 and 12.

New Rejections
Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. Claims 2-5, 7-12, 24-26 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grandoni (US 5,998,420) in view of Hamprecht et al (US 5,591,694) in view of Gordon et al (Of record, J. Med. Chem. 1994, Vol. 37, No. 10, pp. 1385-1401).

Grandoni et al teach sulfonylurea herbicides that read on the claimed compounds (see Figures 3 & 5, for example). The pyrimidine compounds have least three functionalizable atoms, at least one of which is nitrogen, oxygen and/or sulfur and have groups that can be considered tethers (see structures **S**, **T**, **U** and **V** in Figure 5 and compound at the bottom of Figure 6). The building blocks of the library comprise various leaving groups (see column 9, top). In the context of creating better inhibitors of acetolactate synthase (beginning in column 8 and going through the top of column 10), Grandoni et al teach the concept of "combinatorial optimization of inhibitory sulfonylureas" (column 9). The activity of such compounds reads on the limitations of claims 24-26.

Hamprecht et al also teach sulfonylurea herbicides (see Abstract). These compounds also read on those in the claimed mixture and have similar substitution to those of Grandoni. Hamprecht et al teach that compounds with improved properties are needed and that to do so, varying the substituents on the pyrimidine moiety is a preferred method of doing so (see column 2, lines 12-23).

Grandoni and Hamprecht et al lack the teaching of creating a mixture of at least 6 compounds.

However, Gordon et al teaches that “[w]hen small molecule leads for a target have been previously defined...the notion of searching for more potent derivatives among libraries combinatorially enriched in specific pharmacophore analogs is an obvious tactic to pursue” (p.1386 Column 1, 1st full paragraph).

Also, Gordon et al teaches the general principles of combinatorial chemistry and the rationale for creating libraries, see page 1385 and 1397-1401 generally.

Specifically, the notion of intentional biasing as a form of drug design is taught (see page 1401, 1st column). Gordon et al teaches a “spectrum of molecular diversity” (see page 1397, Figure 19) that describes why a library of a certain size would be useful for a variety of different applications.

Therefore, it would have been *prima facie* obvious to one of ordinary skill to create a mixture (i.e. library) of six or more compounds of the claimed type based on the teachings Grandoni and Hamprecht et al as to the synthesis and uses of such compounds and the teachings of Gordon et al regarding libraries. A person of ordinary skill in the art would have been motivated to create libraries to

have large numbers of molecules available for testing for improved properties (see Gordon, page 1398, 1st paragraph).

Response to Arguments

19. Applicant's arguments filed August 17, 2000 have been fully considered but they are moot in view of the new grounds of rejection.

Status of Claims/Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie E. Garcia, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday from 9:30 to 7:00 and alternate Fridays.

22. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie E. Garcia, Ph.D.
November 16, 2000


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